The incidence of staining of permanent teeth by the tetracyclines

J. M. CONCHIE, D.D.S., D.D.P.H., J. D. MUNROE, M.D., C.R.C.P.[C] and
D. O. ANDERSON, M.D., F.R.C.P.[C]

Summary: In this investigation an attempt has been made to determine the relationship between the staining of permanent teeth by tetracycline administered during the period of tooth formation with the dosage of the drug and the duration of therapy. Of 238 subjects whose hospital records indicated ingestion of stated doses of tetracycline, some 49 were seen to have staining which was confirmed by fluorescence, and a further six had staining which did not fluoresce and hence could not be confirmed. A definite relationship between total dosage and staining and duration of administration and staining was established; the condition occurred with greater frequency (in more than one-third of the children) when the total dosage exceeded 3 g. or the duration of treatment was longer than 10 days. However, as staining was seen at all dosage levels, whatever the duration, physicians should continue to follow previous advice and prescribe other antibiotics where possible for children under 8 years of age or for women in the last trimester of pregnancy.

The tetracycline antibiotics were introduced in 1950. Since that time these agents have been used extensively in the management of infectious conditions, especially those of the respiratory tract and middle ear. They have been found to be effective against certain penicillin-resistant organisms. A high level of efficiency accompanied by a comparatively low incidence of adverse side effects has been demonstrated.

In recent years, reports have been published regarding the discolouration of teeth resulting from the administration of tetracyclines during the period of tooth formation. Concern was expressed in some of these reports that tetracyclines might also disturb enamel formation, leading to malformed, hypoplastic teeth. When these conditions occur in the primary teeth, the problem will be resolved by their natural exfoliation; if, however, the secondary teeth are so affected the condition is permanent and therefore much more distressing.

As a result of these observations, the Food and Drug Administration of the United States issued an official statement in April 1963 that tetracyclines could discolour children's teeth if administered to the mother during the last trimester of pregnancy or to the child in the neonatal period, infancy or early childhood.[1]

In June 1963 the Council on Dental Therapeutics of the American Dental Association issued a report on "The Significance of Dental Changes Induced by Tetracycline".[2] It was suggested that physicians might avail themselves of dental consultation regarding the vulnerable periods of tooth formation when use of these drugs would be contraindicated. The report stated that these adverse changes did not appear in every instance, even in long-term therapy. On the other hand, tooth discolouration had been observed as a result of short-term ingestion of tetracyclines. Since no threshold dosage had yet been determined, it was emphasized in the report that all physicians and dentists should be aware of these facts, and that where possible, alternative antibiotics should be employed.

No specific guidelines to the use of tetracyclines in these age groups have been suggested. It was with the object of determining, if possible, the dental risk to the child that this study was planned. We have attempted to determine the proportion of children known to have ingested tetracyclines during the critical periods of tooth formation who now demonstrate staining of the permanent teeth, and to relate this to the age at time of administration, the quantity consumed and the duration of the therapy.

Review of the literature

There are many publications which describe the action of tetracyclines on various tissues of the body. A thorough review of the literature has been published by Johnson.[3] More recently, a special report on the effects of tetracyclines on

J. M. CONCHIE, D.D.S., D.D.P.H., Regional Dental Consultant, Health Branch, Province of British Columbia, 14265-56th Avenue, Surrey, B.C.
J. D. MUNROE, M.D., C.R.C.P.[C], Director, Simon Fraser Health Unit, New Westminster, B.C.
D. O. ANDERSON, M.D., F.R.C.P.[C], Professor, Department of Health Care and Epidemiology, University of British Columbia, Vancouver.
Reprint requests to: Dr. J. M. Conchie, Regional Dental Consultant, Department of Health, Province of British Columbia, 14265-5th Avenue, Surrey, British Columbia.

skeletal growth and dentition was prepared by the Nutrition Committee of the Canadian Paediatric Society.[4]

The first report on tooth discolouration due to the ingestion of tetracyclines was made in 1956 by Shwachman and Schuster.[5] They examined 300 children who had been on therapy for one year or more, and noted that 5% of these children had discoloured deciduous teeth.

Wallman and Hilton[6] noted the association between tetracycline ingestion and subsequent pigmentation of the deciduous teeth, and suggested that this had resulted from large doses of the antibiotic. They observed that the discolouration varied from grey-yellow to dark brown. Harcourt, Johnson and Storey[7] in 1962 demonstrated a similar discolouration in the dentin of permanent teeth which could be detected microscopically in a section of the extracted tooth. It was first noted by Saltzman[8] in 1950 that tetracyclines fluoresced when exposed to ultraviolet light. Milch, Rall and Tobie[9] in 1957, after treating experimental animals with tetracyclines, observed that bone which contained deposits of tetracycline exhibited a characteristic golden-yellow fluorescence under ultraviolet light and that the teeth also displayed sites of fluorescence. Gron and Johannessen[10] in 1961 observed yellow bands of fluorescence which corresponded to the times of administration of tetracyclines in the dentin of teeth of experimental animals. Hilton[11] noted that tetracycline-induced stains in bone turned darker after several weeks and no longer fluoresced. He has suggested that the tetracycline breaks down on prolonged exposure to light, producing an oxidation product that causes the darker discolouration.

Frankel and Hawes[12] in 1964 examined 1724 school-children aged 5 to 10 years, of whom 35 had tetracycline-induced tooth discolouration. In this study they were able to relate the area of discolouration to the layer of tooth crown which was being formed at the time of tetracycline administration. This prevalence rate of 2.3% is similar to that obtained by Hennon[13] in a study of 1707 children of whom 60 (3.5%) showed staining. In their investigations the number of children who had received tetracyclines without developing this discolouration was not determined.

It has been demonstrated by Kutscher *et al.*[14] that tetracyclines may pass through the placental barrier. Hence, staining of the deciduous teeth may result from administration of tetracyclines to the mother during the last trimester of pregnancy.

Mechanism

The precise mechanism whereby tetracyclines are incorporated into the teeth and bones is not clearly understood. However, it appears to be the result of chelation of the tetracycline with calcium ions in the molecular structure.[15] This phenomenon occurs only during the period of the calcification process, and for this reason such an effect on the teeth occurs only during the last trimester of pregnancy and in childhood. The deciduous teeth may be affected up to the age of 10 months, the anterior permanent teeth during the period 6 months to 6 years and the posterior permanent teeth up to 8 years of age.

Methods

In this investigation the names and pertinent details were obtained of children who were reported to have ingested tetracycline in hospital some time during the period of formation of the anterior permanent teeth. These children were examined several years later to determine if the permanent teeth had been affected. All examinations were carried out by the same examiner (J.M.C.).

The Hospital Insurance Service of the Government of the Province of British Columbia kindly provided the admission numbers of children of specified ages who were in hospital in certain years. Their hospital records were then scrutinized to ascertain if any tetracycline drug had been administered. In such instances the following information was noted: patient's name, address, body weight, illness, name of tetracycline preparation, dosage schedule, duration of administration and the total dosage.

The treatment records of children admitted during the years 1957-1961 inclusive, for treatment of infectious conditions, to the Royal Columbian Hospital and St. Mary's Hospital in New Westminster, B.C., and to the Vancouver General Hospital, were reviewed.

The present address of each child and the name of the school attended was then determined from Health Unit records. We were successful in tracing 238 children

TABLE I

Characteristics of groups classified by staining of teeth at time of receiving tetracycline in hospital

Group	*No. of cases*	*No. of treatment series*	*Average age at time of treatment (months)*	*Median duration of treatment (days)*	*Average total weight of drugs received during all treatments*		*Average weight drug received per day at each treatment*		*Average body weight at time of each treatment*	*Average dose per lb. body weight at each treatment*	
					Mean (grams)	*Median (grams)*	*Mean (grams)*	*Median (grams)*		*Mean (grams)*	*Median (grams)*
No staining	183	227	26	6	2.6	2.5	0.25	0.5	26 lbs. 5 oz.	0.08	0.096
Staining	6	9	24	5	3.0	2.5	0.54	0.5	22 lbs. 12 oz.	0.13	0.084
Staining with fluorescence	49	80	25	9	3.3	3.6	0.47	0.5	30 lbs. 6 oz.	0.11	0.117

out of the total of 478 whose records we wished to follow. The dental examinations were carried out during the period 1966-68.

At the time of the dental examination, most of the children were aged 8 to 11 years, by which time the anterior permanent teeth were partially or fully erupted.

The examinations were carried out in the following way: Each child under investigation was accompanied by two control children from the same classroom. The classroom teacher had chosen at random two other children of the same sex with similar physical characteristics to act as controls or standards in the examination. The identity of the children was not known to the examiner, so that the factor of subjective bias would be eliminated. The teeth of all the children were observed under normal daylight conditions. They were then examined using ultraviolet light in a completely darkened room. Under ultraviolet light the tetracycline in the crown of the tooth fluoresces bright golden yellow, whereas the normal tooth appears bluish-white. For this purpose both short-wave and longer-wave ultraviolet lamps were used. Fluorescence was more readily detected with the short-wave lamp (2537 Å).

Statistical methods

Attempts were made to determine if an association existed between staining and a number of hypothesized independent variables, viz. the underlying disease, age at time of administration, weight, dosage and duration of treatment.

As there was no reason to expect that the data would follow the normal (Gaussian) distribution curve, these associations were investigated by non-parametric means such as the chi-square test.

The data presented in the tables of this text were also, where appropriate, tested for statistical significance by the use of Goodman's gamma test.[16] This test is appropriate when the variables have an inherent and meaningful order. For example, fluorescent staining is more staining than no staining, and a dosage of two grams is greater than one gram. The gamma test indicates whether there is a significant relationship between these ordered classes.

Results

There are four different chemical types of tetracyclines: tetracycline, oxytetracycline, chlortetracycline and demethylchlortetracycline. The following brand names under which they are manufactured were those most frequently encountered in this study: tetracycline—Achromycin, Tetracyn and Tetrex; chlortetracycline—Aureomycin; oxytetracycline — Terramycin; demethylchlortetracycline — Declomycin. These are also combined in certain instances with other drugs as in Achrostatin, Mysteclin F and Albamycin T.

Of the 714 children who were examined, 67 had teeth with a degree of staining which was considered by the examiner to be beyond the normal range of colouration. It was confirmed by fluorescence, except in six cases, that this staining was in fact tetracycline-induced. In the case of these six children, the failure to fluoresce may have been due to the oxidation of the tetracycline.

It is of interest to note that 12 of the subjects were in the group of 476 controls. If it is assumed that the controls were a fairly random sample of the normal school population, this would be seen to be comparable with what has been found elsewhere.[12, 13]

Of the 238 subjects who were being investigated, it was noted that there were no dental effects as a result of the tetracycline ther-

TABLE II

Association between disease group at time of largest dosage of tetracycline and staining of teeth in the cohort*

	Fluorescence		*No fluorescence*			
			Staining only	*No staining*	*Total*	
Groups	*No.*	*%*	*No.*	*No.*	*No.*	*%*
1	31	64.6	4	121	125	69.5
2	8	16.7	0	22	22	12.2
3	9	18.7	0	33	33	18.3
Not known	1	—	2	7	9	—
Total	49	100.0	6	183	189	100.0

*χ^2 and γ not significant

TABLE III

Association between age and staining of teeth in the cohort

	Fluorescence		*No fluorescence*			
			Staining only	*No staining*	*Total*	
	No.	*%*	*No.*	*No.*	*No.*	*%*
A. Age at first dosage of tetracycline*						
Less than 1 year	7	14.3	1	19	20	11.5
1	14	28.6	3	46	49	26.8
1½	9	18.3	0	37	37	19.6
2	5	10.2	0	27	27	13.6
2½	7	14.3	0	22	22	12.3
3 years or over	7	14.3	2	31	31	16.2
Not known	0	—	0	1	1	—
Total	49	100.0	6	183	189	100.0
B. Age at largest dosage of tetracycline*						
Less than 1 year	6	12.3	1	16	17	9.0
1	10	20.4	3	40	43	22.9
1½	10	20.4	0	39	39	20.7
2	4	8.2	0	27	27	14.4
2½	8	16.3	0	22	22	11.7
3 years or over	11	22.4	2	38	40	21.3
Not known	0	—	0	1	1	—
Total	49	100.0	6	183	189	100.0

*χ^2 and γ not significant

TABLE IV
Association between weight of child and staining of teeth in the cohort

	Fluorescence		*No fluorescence*			
			Staining only	*No staining*	*Total*	
	No.	*%*	*No.*	*No.*	*No.*	*%*
A. Weight at first dosage of tetracycline*						
10-19 lbs.	6	15.8	1	13	14	10.7
20-24	9	23.7	1	27	28	21.4
25-29	12	31.6	2	42	44	33.6
30 lbs. or more	11	28.9	0	45	45	34.3
Not known	11	—	2	56	58	—
Total	49	100.0	6	183	189	100.0
B. Weight at largest dosage of tetracycline*						
10-24 lbs.	14	35.9	2	38	40	30.5
25-29	9	23.1	2	44	46	35.1
30-34	10	25.6	0	27	27	20.6
35 lbs. or more	6	15.4	0	18	18	13.8
Not known	10	—	2	56	58	—
Total	49	100.0	6	183	189	100.0

*χ^2 and γ not significant

apy in 183. Staining and fluorescence were observed in 49. Staining only, without fluorescence, was seen in six; for statistical purposes these are considered as "no staining", since despite the appearance, the lack of fluorescence implied some doubt as to its cause. The basic data are summarized in Table I.

Association between underlying disease and staining

The disease state at the time of the largest dosage of tetracycline given in hospital was placed in one of three categories by one of us (D.A.): Group 1, lower respiratory; Group 2, upper respiratory including tonsillitis; and Group 3, all other conditions.

No significant association between the disease group and staining of the teeth was found by either the chi square test or the gamma test (Table II). It is reasoned, therefore, that although the nature of the disease as stated is related to hospitalization and to treatment with tetracycline, staining is not directly related to a single disease group.

Causative association between tetracycline administration and staining

The design of the study precluded a control group. It was believed that any relationship between the use of tetracycline and staining of the teeth would be associated with the components of dosage and staining. However, before attempting to establish this relationship it was considered that any association between age and weight and staining should be ruled out. Since the dosage administered to a child is usually adjusted to age and weight by one of the standard formulas, it was reasoned that there should be no association for these factors.

In the following analysis, in order to interpret the results conservatively, the six children with staining but no fluorescence have been included in the group with no staining; they are, however, identified in the association tables.

The frequency distribution of the groups according to age and weight at the time of the first recorded dose of tetracycline given over a period of time in hospital (largest dosage) is shown in Tables III and IV. The total amount of the drug, as indicated in the record during a single hospitalization, was assumed to be the largest dosage. On the basis of either the chi square or gamma test, no association between age or weight of the child at the time of the first or largest dosage could be established.

It was noted that in each category the number of males was greater than females. However, it was determined on the basis of a chi square test that sex was not a significant factor.

Of the 238 subjects investigated, only 11 had been treated in hospital with forms of tetracycline other than tetracycline HCl. It has been stated that the use of oxytetracycline or chlorotetracycline may reduce the incidence of staining. Because of the small numbers involved, it was not possible from this study to draw any conclusions.

The frequency distribution of the cohort is given in Tables V and VI, according to dosage of the drug and duration of its administration

TABLE V
Association between hospital-administered dosage of tetracycline and staining of teeth in the cohort

	Fluorescence		*No fluorescence*			
			Staining only	*No staining*	*Total*	
	No.	*%*	*No.*	*No.*	*No.*	*%*
A. Largest dosage*						
Less than 2 g.	10	20.4	1	60	61	32.6
2	10	20.4	3	52	55	29.4
3	15	30.6	0	31	31	16.6
4 g. or more	14	28.6	2	38	40	21.4
Not known	0	—	0	2	2	—
Total	49	100.0	6	181	189	100.0
B. Total dosage†						
Less than 2 g.	7	14.3	1	57	58	30.9
2	9	18.4	3	49	52	27.7
3	12	24.5	0	29	29	15.4
4	8	16.3	2	28	30	15.9
7 g. or more	13	26.5	0	19	19	10.1
Not known	0	—	0	1	1	—
Total	49	100.0	6	181	189	100.0

*χ^2 = 7.86, d.f. = 3.05>P>.02
γ = 0.2634 .02>P>.01
†χ^2 = 14.80, d.f. = 4.01>P>.001
γ = —0.3731 P<.01

in hospital. In addition to the largest dosage, the total dosage was determined by summation of all the charted tetracycline. A highly significant association was found between staining and both dosage and duration of treatment. The gamma test was also significant and indicates that fluorescence was more common at higher dosage or treatment-duration levels.

Tables V and VI indicate that a dose-response relationship actually exists in the children we studied who received tetracycline in hospital.*

It was believed that the levels recorded in Tables V and VI might not be valid: children who were given tetracycline in hospital might be more likely to receive it at home. For that reason, a follow-back study was undertaken of the 49 children with fluorescence; the physician in attendance was asked if the child had received further treatment with tetracycline after leaving hospital. The follow-up was not very successful because few physicians recorded treatment in sufficient detail to be certain of the actual amount of additional tetracycline. In many cases the physician was no longer practising in the district. In other cases the name of the regular family physician at the time could not be discovered. However, of 14 children whose records were deemed adequate by the attending physician, only five had received extra tetracycline.

TABLE VII
Association between hospital-administered tetracycline and fluorescence of the teeth in the cohort

	Fluorescence		*No fluorescence**		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Total duration of largest dosage 1-9 days						
Largest dosage:						
Less than 3 g.	17	13.1	113	86.9	130	100.0
3 g. or more	17	25.3	50	74.6	67	100.0
Total duration of largest dosage 10 days or over						
Largest dosage:						
Less than 3 g.	3	50.0	3	50.0	6	100.0
3 g. or more	12	34.3	23	65.7	35	100.0
Total duration of all hospital-administered tetracycline 1-9 days						
Total dosage:						
Less than 3 g.	13	10.9	106	89.1	119	100.0
3 g. or more	13	24.5	40	75.7	53	100.0
Total duration of all hospital-administered tetracycline 10 days or over						
Total dosage:						
Less than 3 g.	3	42.9	4	57.1	7	100.0
3 g. or more	20	33.9	39	66.1	59	100.0

*Includes children with staining only

An attempt was then made to determine whether the dosage or the duration of dosage was the more important factor. The basic data are shown in Table VII. As might be expected, only a small number of children were given a small dosage over a long period of time; nevertheless the dose-response relationship was clear. The proportion showing staining rose above 33% if therapy was continued for more than 10 days, or if the dosage exceeded 3 g.

It appears, therefore, that the chances of the permanent teeth being stained by tetracyline are considerably greater if larger doses are given and if the therapy is of longer duration. However, this investigation has demonstrated that staining may occur when a small dosage is given for a short period of time. Other unknown intrinsic factors, possibly genetic, may have some influence, since at these low dosages and for such short time periods the dose and duration appear to act independently.

Implications

As the discolouration is permanent, this iatrogenic effect, which may occur in one-third of pediatric patients, should always be considered when prescribing a tetracycline

*The statistical significance of the data in Tables V and VI and the lack of significance of the data in Tables III and IV were confirmed by the Mann-Whitney U-test of the distribution of data. This test does not depend on *a priori* classes or a normal distribution.

TABLE VI
Association between duration of hospital-administered tetracycline and staining of the teeth in the cohort

	Fluoresence		*No fluorescence*			
			Staining only	*No staining*	*Total*	
	No.	*%*	*No.*	*No.*	*No.*	*%*
A. Total duration of largest dosage*						
1-4 days	9	18.4	2	66	68	36.6
5-9	25	51.0	3	92	95	51.0
10 or more days	15	30.6	0	23	23	12.4
Not known	0	—	1	2	3	—
Total	49	100.0	6	183	189	100.0
B. Total duration of all hospital-administered tetracycline†						
1-4 days	7	14.3	2	61	63	33.7
5-9	19	38.8	3	80	83	44.4
10-14 days	10	20.4	0	25	25	13.3
15 or more days	13	26.5	0	16	16	8.6
Not known	0	—	1	1	2	—
Total	49	100.0	6	183	189	100.0

*$\chi^2 = 11.90$, d.f. = 2 $.01>P>.001$
$\gamma = -0.4338$ $P<.01$
†$\chi^2 = 16.72$, d.f. = 3 $P<.001$
$\gamma = -0.4595$ $P<.001$

drug. Because of its usefulness in many diseases of early childhood, the need for using tetracycline may outweigh the risk of its administration. The physician should carefully record the reasons for prescribing this drug so that he may be able to explain to parents, in later years, why there was no alternative.

While the drug companies point out that staining may occur, we would like to emphasize the adverse psychological effect this has upon the child; many of these children become extremely sensitive about the disfigurement of their teeth.

Résumé

La fréquence de la coloration des dents permanentes par les tétracyclines

Notre étude avait pour objet d'essayer d'établir un lien entre la coloration des dents permanentes par l'administration de tétracycline durant la période de formation des dents et la posologie (dose du médicament et durée du traitement). Sur 238 sujets dont on savait qu'ils avaient reçu des doses exactes de tétracycline, on en a trouvé 49 dont les dents étaient colorées (coloration confirmée par fluorescence) et six autres dont les dents étaient également colorées mais qui ne réagissaient pas à la lumière fluorescente. Ces derniers cas n'ont donc pu être confirmés. Cette relation a pu être nettement établie, en ce qui concerne la coloration, la posologie et la durée du traitement; elle a été observée plus fréquemment et chez plus d'un tiers des enfants qui avaient une posologie globale de plus de 3 g ou qui avaient été traités pendant plus de 10 jours. Cependant, comme la coloration était visible à tous les paliers posologiques, nous recommandons aux médecins de suivre les conseils antérieurs, c'est-à-dire de prescrire d'autres antibiotiques quand la chose est possible, aux enfants de moins de 8 ans ou à des femmes enceintes pendant la dernier trimestre de leur grossesse.

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Mechanism of Hepatic Dysfunction Following Shock and Trauma

Twelve patients, representing 2% of a group of patients with shock and major trauma, developed a syndrome of moderate to severe jaundice, first appearing two to ten days after injury. Although the serum analyses suggested obstructive jaundice with conjugated hyperbilirubinemia and elevated alkaline phosphatase, there was no evidence of extrahepatic obstruction. Resolution of the jaundice with no apparent residual liver damage was the rule in the survivors. Histologic examination of the liver typically showed centrilobular congestion and occasionally necrosis with bile stasis. The primary mechanism of the jaundice appears to be a hepatic cellular excretory defect resembling intrahepatic cholestasis, which probably is due to hepatic anoxia. The increased bilirubin load provided by transfused and extravasated blood, which in the normal liver would cause only mild jaundice, results in more severe and prolonged jaundice in the patient with an anoxia-damaged liver.

Jaundice seen in patients following shock and trauma is of little consequence in itself but is indicative of impairment of all aspects of liver function, and the ultimate outcome in severe shock is profoundly affected by hepatic functional impairment. In this sense, jaundice is a grave prognostic sign in the patient recovering from shock.—G. Nunes, F. W. Blaisdell and W. Margaretten: *Arch. Surg. (Chicago)*, 100: 546, 1970 (May).